November 23, 2009

Dr. Barbara Shane
Executive Secretary, Board of Scientific Counselors
NIEHS, NTP Office of Liaison, Policy and Review
P.O. Box 12233, K2–03
Research Triangle Park, NC 27709

Delivery via e-mail to *shane@niehs.nih.gov*

Dear Dr. Shane:

Subject: Supplementary Information for the Review off Hydroquinone During the December 9-10, 2009 Meeting of the NTP Board of Scientific Counselors

In response to the October 23, 2009 Federal Register Notice announcing the December 9-10, 2009 meeting of the NTP Board of Scientific Counselors (BSC) [1], the Hydroquinone Group[2] is pleased to provide the enclosed supplementary information regarding hydroquinone. As part of their product stewardship programs, member companies of the Hydroquinone Group have funded research to develop new toxicological and pharmacokinetic data pertinent to an assessment of the safety of hydroquinone.

By way of these comments, we are providing information on published and unpublished information that may be of interest to the NTP Board during its deliberations on hydroquinone. In particular, we are providing information regarding studies on reproductive and developmental toxicity, toxicokinetics, and carcinogenicity. These studies are either completed, undergoing peer-review for publication, or included in post-marketing commitments made to the FDA. The studies address the inconsistencies and data gaps mentioned in the NTP Research Concept document.

Please feel free to contact us if you have any questions regarding this information or on hydroquinone in general. We thank you for this opportunity to provide this information to the NTP and to the NTP Board.

Sincerely,

Betsy Carlton (es)

Betsy Carlton, PhD, DABT
Chair, Hydroquinone Group
c/o Rhodia Inc.
5171 Glenwood Ave, Suite 402
Raleigh, NC 27612
betsy.carlton@bluestarsilicones.com

[1] 74 Fed. Reg. 54821.
[2] The Hydroquinone Group is comprised of major global manufacturers of hydroquinone

Supplementary Information for the Review off Hydroquinone During the December 9-10, 2009 Meeting of the NTP Board of Scientific Counselors

In its Fifth Report to the Administrator of the US Environmental Protection Agency (EPA) (44 FR 70664) published in 1979, the Toxic Substances Control Act (TSCA) Interagency Testing Committee (ITC) designated hydroquinone for further health effects testing including carcinogenicity, teratogenicity, and epidemiology.

Subsequently, EPA published a final rule (50 FR 53145) that required testing "to evaluate hydroquinone's toxicokinetics and to determine its potential to produce nervous system, reproductive and teratogenic effects". The EPA's decision to require testing for reproductive and teratogenic effects was based on its analysis of publications from the 1950s and1960s. These same publications appear to be the basis for the proposed NTP Research Concept and the statement in the Concept document regarding potential reproductive and developmental toxicity of hydroquinone.

As part of the TSCA test rule for hydroquinone, EPA required that the studies to address its concern about possible reproductive toxicity and teratogenicity from hydroquinone exposure be conducted according to Agency-approved guidelines and under Good Laboratory Practice Standards (GLP). All of the TSCA test rule results for reproductive and teratogenic endpoints were published in the peer-reviewed literature in addition to being delivered to the EPA, which also conducted an onsite inspection of selected raw data for the studies. The inconsistencies mentioned in the NTP Research Concept document result from the differences observed between the early (1950s and1960s) studies that were <u>not</u> conducted under TSCA test rule and GLP requirements and studies that were conducted under TSCA requirements. The TSCA-related studies include a rabbit developmental toxicity study (Murphy et al., 1992), a rodent developmental toxicity study (Krasavage et al., 1992), and a rodent two-generation reproduction study (Blacker et al., 1993).

As originally requested by the ITC, an epidemiology study was conducted for hydroquinone, although it was not part of the TSCA test rule. The study included an occupational population with long-term exposure to hydroquinone dust, via both inhalation and dermal exposures, and inhalation exposure to p-benzoquinone vapor (Pifer et al., 1995).

Since completion of the toxicokinetic testing required under the TSCA rule, additional toxicokinetic studies have been published (Corley et al., 2000; Poet et al., 2004) and a study adding a dermal exposure component to the toxicokinetic modeling for hydroquinone has been submitted for publication (Poet et al., 2009). A mode-of-action determination has recently been completed by McGregor (2007) following an internationally agreed protocol.

While there is no long-term dermal chronic toxicity study of hydroquinone, a 90-day subchronic study with hydroquinone in a skin lightener formulation in rats has been published (David et al., 1998).

In addition to the above-mentioned studies, there are two ongoing studies with hydroquinone in a skin lightening formulation, which also includes fluocinolone acetonide and tretinoin. While the combination drug is not solely a hydroquinone exposure, the additional drugs involved are not expected to decrease the dermal absorption of hydroquinone. Both of these studies are related to post-marketing commitments made to the FDA by the manufacturer of a skin lightener. One of the studies involves human pregnancy outcome data from use of the skin lightener. The status of this study according to an FDA internet website is "Pending." The second study includes dermal cancer bioassays in rats and mice including pigmented animals. This study is nearing completion and, according to the FDA reporting method on its internet website, the study is on-schedule. Information on these studies may be available from the FDA for product NDA/BLA Number 21112.

Abstracts of the cited literature are appended to these comments.

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FUNDAMENTAL AND APPLIED TOXICOLOGY 21, 420–424 (1993)

A Two-Generation Reproduction Study with Hydroquinone in Rats[1,2]

A. M. BLACKER,*,[3] R. E. SCHROEDER,† J. C. ENGLISH,‡ S. J. MURPHY,§ W. J. KRASAVAGE,‡ AND G. S. SIMON*

*Rhône-Poulenc Inc., P.O. Box 12014, Research Triangle Park, North Carolina 27709; †Pharmaco-LSR, East Millstone, New Jersey; ‡Eastman Kodak Company, Rochester, New York; and §The Goodyear Tire & Rubber Company, Akron, Ohio

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A Two-Generation Reproduction Study with Hydroquinone in Rats. BLACKER, A. M., SCHROEDER, R. E., ENGLISH, J. C., MURPHY, S. J., KRASAVAGE, W. J., AND SIMON, G. S. (1993). *Fundam. Appl. Toxicol.* 21, 420–424.

The effects of hydroquinone (HQ) on reproductive performance and fertility were assessed in a two-generation study with CD Sprague–Dawley rats (one litter per generation). HQ was administered in an aqueous solution by gavage at doses of 0, 15, 50, and 150 mg/kg/day. F0 and F1 parental animals were dosed daily for at least 10 weeks prior to cohabitation, during cohabitation, and until scheduled termination. At all dose levels tested, no adverse effects were observed on feed consumption, survival, or reproductive parameters for the F0 or F1 parental animals. Mild, transient tremors were observed shortly after dosing at 150 mg/kg/day in several F0 and F1 parental animals and in a single F0 male at 50 mg/kg/day. These tremors occurred infrequently and were considered to be due to an acute stimulatory effect of HQ on the nervous system. Body weights for F0 and F1 parental females were similar between all dose groups throughout the study. Body weights for F0 parental males were also comparable to those of control throughout the study. Statistically significant differences in body weights were noted for the F1 parental males in the 50 and 150 mg/kg/day dose groups at several intervals during the premating, mating, and postmating periods. No treatment-related effects on pup weight, sex distribution, or survival were noted for pups of either generation. Upon postmortem examination, no treatment-related gross lesions were observed in either the F0 or F1 parental animals or their weanlings. Histopathologic examination of reproductive tissues and pituitary glands from high-dose F0 and F1 parental animals did not reveal any changes related to treatment with HQ. Thus, no adverse effects on reproduction or fertility were observed in either generation at any dose level, and the results of the present study indicate that HQ is not a selective reproductive toxicant. The no observed effect levels for general and reproductive toxicity are 15 and 150 mg/kg/day, respectively.
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Hydroquinone (HQ) is widely distributed in nature and is found in the leaves, bark, and fruit of a number of plants and in a number of insects (Harbison and Belly, 1982). Due to its reducing properties, HQ is used industrially as an intermediate in the production of rubber chemicals, dyes, pigments, feed antioxidants, and monomer inhibitors, and as a developer in black-and-white photographic processes. Small amounts of HQ are also used in cosmetic preparations (USEPA, 1985).

Little information on potential reproductive effects following repeated exposure to HQ is available. In 1958, Racz *et al.* observed a prolonged diestrus phase of the estrus cycle in female rats receiving 200 mg HQ/kg/day by gavage for 14 days. However, evidence of overt toxicity was observed at this dose and consisted of tremors, convulsions, and 30% mortality. Racz *et al.* further reported that animals treated at lower doses, which did not produce toxicity, exhibited equivocal results. In another study, an increase in fetal resorptions was observed in rats receiving a total of 500 mg HQ in the diet during pregnancy (Telford *et al.*, 1962). Male rats receiving 300 mg HQ/kg/day sc for 51 days were found to have the following: reduced testes, epididymides, seminal vesicle, and adrenal gland weights; histologic changes in the testes; and reduced reproductive performance (Skalka, 1965). However, no adverse effects on fertility, gestation length, mean litter size, or viability were observed following administration of HQ to female rats at dietary levels up to 3000 ppm (Ames *et al.*, 1956). In an unpublished dominant lethal study (Krasavage, 1984), hydroquinone was administered 5 days per week to male rats by gavage at doses of 30, 100, or 300 mg/kg/day in distilled water. Males were mated with untreated virgin females during the 2-week period immediately after the 10-week dosing period. Despite evidence of overt toxicity at 300 mg/kg/day (spastic gait, tremors, convulsions, and mortality), insemination and pregnancy rates and mean number of implanta-

[1] Presented in part at the 31st Annual Meeting of The Teratology Society, Boca Raton, Florida, June, 1991.

[2] This study was sponsored by the Chemical Manufacturers Association Hydroquinone Panel under section 4(a) of the Toxic Substances Control Act, and was conducted in accordance with the requirements of the Hydroquinone Final Test Rule (50 FR 53145-53165, December 30, 1985) and the Hydroquinone Final Test Standards and Reporting Requirements (52 FR 19868-19870, May 28, 1987). The member companies of the Hydroquinone Panel are Eastman Kodak Company, The Goodyear Tire & Rubber Co., Mitsui Petrochemical Industries, Ltd., and Rhône-Poulenc Inc.

[3] To whom correspondence and reprint requests should be addressed. Fax: (919) 549-2925.

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Development of a Physiologically Based Pharmacokinetic Model for Hydroquinone

R. A. Corley,* J. C. English,† T. S. Hill,† L. A. Fiorica,† and D. A. Morgott†

*Battelle Memorial Institute, Pacific Northwest Division, Molecular Biosciences Department, Chemical Dosimetry, P.O. Box 999, P7-59, Richland, Washington 99352; and †Health and Environment Laboratories, Eastman Kodak Company, 1100 Ridgeway Avenue, Rochester, New York 14652-6272

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Development of a Physiologically Based Pharmacokinetic Model for Hydroquinone. Corley, R. A., English, J. C., Hill, T. S., Fiorica, L. A., and Morgott, D. A. (2000). *Toxicol. Appl. Pharmacol.* 165, 163–174.

Hydroquinone (HQ) produces nephrotoxicity and renal tubular adenomas in male F344 rats following 2 years of oral dosing. Female F344 and SD rats are comparatively resistant to these effects. Nephrotoxicity and tumorigenicity have been associated with a minor glutathione conjugation pathway following the oxidation of HQ to benzoquinone (BQ). The majority of administered doses (90–99%) consists of glucuronide and sulfate conjugates of HQ. An initial physiologically based pharmacokinetic model was developed to characterize the role of kinetics in the strain differences observed in HQ-induced renal toxicity and tumorigenicity. Partition coefficients, protein-binding, and metabolic rate constants were determined directly or estimated from a series of *in vivo* and *in vitro* studies. Metabolism was confined to the liver and GI tract. The total flux through the glutathione pathway represented the "internal dose" of HQ for nephrotoxicity. Simulations were compared to a variety of data from male and female F344 rats, male SD rats, and a single male human volunteer. Simulations of intraperitoneal administration resulted in higher amounts of glutathione conjugates than comparable oral doses. This was consistent with protein-binding and toxicity studies and emphasized the importance of first-pass GI tract metabolism. In addition, male F344 rats were predicted to form more total glutathione conjugates than SD rats at equivalent dose levels, which was also consistent with the observed strain differences in renal toxicity. This model represents the first stage in the development of a biologically based dose–response model for improving the scientific basis for human health risk assessments of HQ. © 2000 Academic Press

Key Words: **Hydroquinone; PBPK model; renal toxicity; glutathione conjugates.**

Hydroquinone (1,4-benzenediol; HQ) is an important industrial chemical used as a reducing agent in photographic development, an antioxidant in the manufacture of rubber, a polymerization inhibitor for vinyl and acrylic monomers, and a depigmenting agent in dermatologic preparations for the treatment of skin blemishes. HQ also occurs naturally in cigarette smoke, the leaves and bark of several plant species as a component of glucopyranoside, arbutin, and plant-derived foods such as coffee, wheat-based products, and red wine (Deisinger and English, 1999).

The widespread industrial and consumer use of HQ has resulted in considerable toxicological research. An increased incidence in renal adenomas was observed in male F344 rats in two chronic bioassays (NTP, 1989 reviewed by Kari *et al.*, 1992; Shibata *et al.*, 1991). Kidney tumors were not observed in female rats or in male and female B6C3F1 mice. Findings of mononuclear cell leukemia in female F344 rats and liver adenomas in B6C3F1 mice were not consistent between the two studies. Early studies with Sprague–Dawley rats (Carlson and Brewer, 1953) did not report any treatment-related tumors. Results from the various bioassays with HQ have been reviewed elsewhere (Whysner *et al.*, 1995).

While the mechanism(s) for the most consistent findings from the chronic bioassays (nephrotoxicity and tumorigenicity in male F344 rats) have not been clearly established, they have been shown to occur only in regions of the kidney significantly affected by chronic progressive nephropathy (CPN). Hard *et al.* (1997) suggested that HQ exacerbation of CPN coupled with compensatory cellular regeneration (tubule proliferation) is the primary mode of action for HQ-induced renal tumors in male F344 rats. Recent studies with the Eker rat, which carries a germline mutation in the Tsc-2 tumor suppressor gene, suggests that the loss of Tsc-2 gene function and the over-expression of TGF-α may also play a role in tumor development (Yoon *et al.*, 1999).

Metabolism to reactive intermediates is clearly involved in the renal toxicity and exacerbation of CPN associated with HQ ingestion. The formation of benzoquinone (BQ) is the first critical step toward the formation of toxic metabolites (see Fig. 1). While redox cycling of HQ ↔ BQ may increase the oxidative stress associated with HQ toxicity by forming reactive oxygen species and consuming cellular reducing equivalents, the major competitive metabolic routes for HQ, glucuronide and sulfate conjugation, apparently short-circuit the redox cycling. As a result, glutathione conjugation of BQ appears to

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Lack of Nephrotoxicity and Renal Cell Proliferation Following Subchronic Dermal Application of a Hydroquinone Cream

R. M. DAVID[1]*, J. C. ENGLISH[1], L. C. TOTMAN[2], C. MOYER[3] and J. L. O'DONOGHUE[1]

[1]Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY 14652-6272, [2]Nonprescription Drug Manufacturers Association, 1150 Connecticut Ave, NW, Washington, DC 20036 and [3]Labpath Ltd, 9950 Concord Church Rd, Lewisville, NC 27023, USA

(Accepted 10 December 1997)

Abstract—Hydroquinone (HQ) is used in over-the-counter formulations of skin-lightening creams sold in the United States and European Union. HQ was introduced into these formulations to provide a safe and effective alternative to mercury and other less effective ingredients. Recent studies involving subchronic oral exposure of male F344 rats to HQ have shown nephrotoxicity and renal tubule cell proliferation (English *et al.*, 1994), while chronic exposures of male F344 rats were reported to cause renal cell adenomas (NTP, 1989). Previous subchronic dermal toxicity studies (CTFA, 1986; NTP, 1989) with HQ failed to detect nephrotoxicity; however, these studies were not specifically designed to assess renal structure and function. More sensitive endpoints were used in the present subchronic study to address concerns over potential toxicity from repeated dermal exposure to HQ. Male and female F344 rats were given topical applications with 0, 2.0, 3.5, or 5.0% HQ in an oil-in-water emulsion cream for 13 wk (5 days/wk). Body weights, feed consumption and water consumption were monitored, and animals were observed for clinical signs of toxicity and dermal irritation. Blood taken at termination was analysed for haematological and clinical chemistry effects. Erythema, which abated when exposure stopped, was the only dermatological effect seen at the HQ-cream application sites. Cell proliferation in the kidneys was evaluated after 3, 6 and 13 wk of treatment using bromodeoxyuridine (BrdU) labelling, but no changes indicative of sustained cell proliferation were seen. The renal histopathological lesions noted after oral exposure to HQ were not present after dermal exposure. Thus, topical exposure to HQ does not result in the renal toxicity observed in previous studies with F344 rats given HQ orally. © *1998 Elsevier Science Ltd. All rights reserved*

Abbreviations: AAP = alanine aminopeptidase; ALT = alanine aminotransferase; BrdU = bromodeoxyuridine; CTFA = Cosmetics, Toiletries, and Fragrance Association; EDTA = ethylenediaminetetraacetic acid; GGT = γ-glutamyl transpeptidase; HQ = hydroquinone; LI = labelling index; NTP = National Toxicology Program; PBS = phosphate buffered saline; SDH = sorbitol dehydrogenase.

INTRODUCTION

Hydroquinone (HQ) is an antioxidant that is primarily used in industrial and commercial applications. A minor use for HQ, however, is as an active ingredient in skin-lightening products. These products are oil-in-water emulsion creams for topical application sold as over-the-counter and prescription drugs to reduce post-inflammatory hyperpigmentation and other forms of disfiguring hyperpigmentation. A Food and Drug Administration (FDA) panel that reviewed the use of skin-lightening creams found HQ to be the only active ingredient considered effective for skin lightening and determined that prolonged use of HQ-containing creams was safe provided the products did not exceed a concentration of 2% HQ (w/v) (FDA, 1978 and 1982). HQ had been introduced into skin-lightening products to replace mercury and a number of ineffective ingredients which had potentially harmful side-effects.

Recently, concern has been expressed over abuse of such preparations and the health hazards associated with long-term use of creams containing HQ at concentrations greater than 2% (IPCS, 1994). Repeated application of some skin-lightening

*Author for correspondence.

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Hydroquinone: A Developmental Toxicity Study in Rats[1]

WALTER J. KRASAVAGE,* ANN M. BLACKER,† J. CAROLINE ENGLISH,* AND SUSAN J. MURPHY‡

*Eastman Kodak Company, Rochester, New York 14652-3615; †Rhône-Poulenc Incorporated, Research Triangle Park, North Carolina 27709; and ‡The Goodyear Tire & Rubber Company, Akron, Ohio 44305

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Hydroquinone: A Developmental Toxicity Study in Rats. KRASAVAGE, W. J., BLACKER, A. M., ENGLISH, J. C., AND MURPHY, S. J. (1992). *Fundam. Appl. Toxicol.* 18, 370–375.

To determine the potential developmental toxicity of hydroquinone (HQ), pregnant rats (COBS-CD-BR) were given 0, 30, 100, or 300 mg/kg HQ by gavage on the 6th through the 15th days of gestation. Maternal effects included a slight, but significant ($p < 0.05$), reduction in body weight gain and feed consumption for the 300 mg/kg HQ dams. Reproductive indices, i.e., pregnancy rate, numbers of corpora lutea, implantation sites, viable fetuses, and early and late resorptions, fetal sex ratio, pre- and postimplantation losses, and gravid uterine weights, were not affected by treatment with HQ. A slightly reduced ($p < 0.05$) mean fetal body weight seen at the 300 mg/kg dose level was associated with the slightly reduced body weight gain seen for the dams at this dose level. Gross external, internal soft tissue, and skeletal examinations of the fetuses revealed no HQ-related malformations. The incidences of gross external variations (small hematomas) and internal soft tissue variations (dilated renal pelvis, hydronephrosis, and hydroureter) in the HQ-treated litters were not statistically different from the control incidences. Skeletal variations (delayed ossification of membranous skull bones, hyoid bone, thoracic centra 1–3, sacral arches 3 and 4, and bilobed thoracic centra 9–13) were seen with similar frequency in the control and HQ-treated groups. A statistically significant increase in the incidence of total common vertebral variations seen at the 300 mg/kg HQ dose level was not considered toxicologically significant. The incidences of total skeletal variations were not statistically different between the control and the HQ-treated groups. It is concluded that HQ was not selectively toxic to the developing rat conceptus and, thus, appears not to have the properties of a developmental toxicant. The no-observable-effect level for both maternal and developmental toxicity was 100 mg/kg, whereas 300 mg/kg was the no-observable-adverse-effect level. © 1992 Society of Toxicology.

Hydroquinone (HQ) acts chemically as a reducing agent. It is used as a developing agent in the photographic industry, as a chemical intermediate in the rubber industry, and as an antioxidant or stabilizer in materials which polymerize in the presence of oxidizing agents. HQ is also used in small amounts in dermatologic preparations as a bleach for hyperpigmented skin and is found in nature in certain plants and soils. In 1985, hydroquinone was the subject of a U.S. Environmental Protection Agency TSCA Section 4 Test Rule which mandated that HQ be tested for reproductive and developmental toxicity. The basis for this required testing was the lack of adequate data for evaluation of potential developmental and reproductive effects of HQ. Reports of four published and one unpublished reproductive study were available at that time. Ames *et al.* (1956) fed HQ at levels of 0, 0.003, and 0.3% in the diet to female rats for 10 days prior to mating and found no effects on reproduction. Racz *et al.* (1958) administered HQ to female rats at 200 mg/kg over a 14-day period. The estrus cycles of the animals were affected (all remained in diestrus). However, this dose was highly toxic, causing tremors and clonic seizures and death in some animals due to respiratory paralysis after the fourth or fifth treatment. Lower doses of 100 or 50 mg/kg HQ did not produce the toxic effects seen at 200 mg/kg, and the effect on the estrus cycle was equivocal. Telford *et al.* (1962) gave an unknown dose of HQ in the diet to inseminated female rats and reported an increased number of resorptions compared to a negative control group. Skalka (1965) injected male rats subcutaneously with 100 mg/kg/day HQ for 51 days and reported reduced testes, epididymis, seminal vesicle, and adrenal gland weights, histologic changes in the testes, and reduced reproductive performance.

Finally, in an unpublished study, Krasavage (1984) gave male rats doses of 30, 100, or 300 mg/kg HQ by gavage in a dominant lethal assay and found no effects on male fertility and no dominant lethality. In response to the EPA ruling, a consortium of chemical companies (Eastman Kodak Company, The Goodyear Tire and Rubber Company, Rhone-Poulenc Incorporated, and Mitsui Petrochemical Industries, Ltd.), under the sponsorship of the Chemical Manufacturers Association, undertook a series of studies to determine the possible adverse effects of HQ on reproduction and fetal development. Blacker *et al.* (1991) reported no adverse effects of HQ on the fertility of male and female rats treated through

[1] This study was conducted in the Health and Environment Laboratories, Eastman Kodak Company. Some of the data were presented in a poster session at the 30th Annual Meeting of the Society of Toxicology in Dallas, Texas, February 25 to March 1, 1991.

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Hydroquinone: An Evaluation of the Human Risks from its Carcinogenic and Mutagenic Properties

Douglas McGregor
Toxicity Evaluation Consultants, Aberdour, Scotland, United Kingdom

The toxicology of hydroquinone has been reviewed on a number of previous occasions. This review targets its potential for carcinogenicity and possible modes of carcinogenic action. The evaluation made by IARC (1999) of its carcinogenic risk to humans was that hydroquinone is *not classifiable as to its carcinogenicity to humans (Group 3)*. This evaluation was based on *inadequate evidence* in humans and *limited evidence* in experimental animals. The epidemiological information comes from four cohort studies involving occupational exposures. A cohort of lithographers, some of whom had worked with hydroquinone, had an excess of malignant melanoma based on five cases, but only two of the cases had reported exposure to hydroquinone. In a study of photographic processors the number of exposed individuals was uncertain and the numbers of cases of individual cancer sites were small. In view of the statistical power limitations of these studies for individual diagnostic categories of cancers, they are not considered to be informative with regard to the carcinogenicity of hydroquinone. A cohort of workers with definite and lengthy exposure to hydroquinone, during either its manufacture or its use, had low cancer rates compared with two comparison populations; the reason for the lower than expected rates is unclear. In a motion picture film processing cohort there were significant excess malignancies of the respiratory system among workers engaged in developing, where there was exposure to hydroquinone as well as other chemicals. There was no information on tobacco smoking habits and no dose-response relationship. Hydroquinone has been shown reproducibly to induce benign neoplasms in the kidneys of male F344 rats dosed orally either by gavage (25 and 50 mg/kg body weight) or diet (0.8%). The gavage study has been evaluated in considerable detail. This evaluation showed that all renal tubule adenomas and all cases of renal tubule atypical hyperplasia occurred in areas of severe or end-stage chronic progressive nephropathy and that the neoplasms were not otherwise confined to any particular part of the kidney. It is likely that the mode of carcinogenic action of hydroquinone is exacerbation of this natural disease process. Hydroquinone is mutagenic in vitro and in vivo, having caused genotoxicity or chromosomal aberrations in rodent bone-marrow cells. At least a portion, if not all, of the chromosomal effects are caused by interference by hydroquinone or its metabolites with chromosomal segregation, probably due to interaction with mitotic spindle proteins. However, the dose routes used to demonstrate these effects in almost all of the studies in vivo were intraperitoneal or subcutaneous injection, which were considered inappropriate. There were five studies by the oral route. These included a mouse bone-marrow cell micronucleus test in which a weak, marginally positive response was obtained following a single oral dose of 80 mg/kg body weight. The remaining oral route studies all showed no significant effect. They included a mouse bone-marrow cell micronucleus test in which there was no genotoxic activity after exposure to a diet containing 0.8% hydroquinone for 6 days; two ^{32}P-post-labeling assays, one with targets of Zymbal gland, liver, and spleen in Sprague-Dawley rats, the other with the kidney as target in F344 rats; and the last oral assay was for 8-hydroxydeoxyguanosine adducts in F344 rat kidney DNA. Thus, the evidence (and the database) for any genotoxic effect in vivo is sparse and none has been observed in kidney. While glutathione conjugates could be responsible for the tumor induction, careful histology seems to show that the most actively toxic of several glutathione compounds tested, 2,3,5-triglutathion-*S*-yl hydroquinone, targets a very specific region of the kidney, the

Address correspondence to Douglas McGregor, Toxicity Evaluation Consultants, 38 Shore Road, Aberdour KY30TU, Scotland, UK. E-mail: mcgregortec@btinternet.com

outer stripe of the outer medulla (OSOM), whereas hydroquinone-associated adenomas are more randomly distributed and occur in the cortex as well as the medulla. A nongenotoxic mode of action that involves exacerbation of a spontaneously occurring rodent renal disease, chronic progressive nephropathy (CPN), is proposed and evaluated. This disease is particularly prominent in male rats and the evidence is consistent with an absence of any human counterpart; therefore, the increased incidence of renal tubule adenomas in hydroquinone-dosed male rats is without human consequence.

Keywords Chronic Progressive Nephropathy, Human Kidney, Hydroquinone, IPCS Framework, Metabolism, Mutagens, Rodent Carcinogens

1. INTRODUCTION

The toxicology of hydroquinone (CAS No. 123-31-9; synonyms *p*-benzenediol; 1,4-benzenediol; dihydroxybenzene; 1,4-dihydroxybenzene; quinol) has been comprehensively reviewed on several occasions, by WHO (1994), Whysner et al. (1995), DeCaprio (1999), and IARC (1999). The evaluation made by IARC (1999) of its carcinogenic risk to humans was that hydroquinone is *not classifiable as to its carcinogenicity to humans (Group 3)*. This evaluation was based on *inadequate evidence* in humans and *limited evidence* in experimental animals. This conclusion was similar to that of WHO (1994).

In this current, more focused review, descriptions of the currently available data on carcinogenesis and mutagenesis are summarized, together with information from studies on the kinetics and nonneoplastic effects of hydroquinone that may be relevant to an evaluation of the human carcinogenic risk that the chemical may present. These conclusions are that hydroquinone is tumorigenic, in that benign neoplasms have been reproducibly induced in male F344 rat kidney. Possible modes of action (MOA) are analyzed using the IPCS Framework (Boobis et al., 2006), from which it is concluded that these tumors arose as a result of exacerbated chronic progressive nephropathy (CPN). This appears to be a rat-specific disease that begins within the first 3 months of life and progresses to become an important cause of death among older rats. It also appears to have no human counterpart and, therefore, no human consequence. Hydroquinone is mutagenic in vitro and in vivo, but the dose route used to demonstrate the in vivo activity is inappropriate and exposure by more appropriate routes, methods and doses allow protective mechanisms to contain the potentially damaging effect of the oxidative properties of hydroquinone.

A. Basic Properties of Hydroquinone

Hydroquinone (MW 110.1) is a white crystalline substance, but industrial use grades may be light grey or light tan, with a melting point of 173–174°C. The specific gravity is 1.332 at 15°C, and the vapor pressure is 2.4×10^{-3} Pa (1.8×10^{-5} mm Hg) at 25°C. It is highly soluble in water (70 g/L at 25°C) and the log *n*-octanol/water partition coefficient is 0.59. It is a reducing agent with an electrochemical potential (E°) of +286 mV for the benzoquinone/hydroquinone (Q/H_2Q) redox couple at 25°C and pH 7.0 and under constant conditions (WHO, 1994). Hydroquinone can be encountered in solid form or in solution during its production and use (NIOSH, 1978). In spite of its low vapor pressure, inhalation exposure remains a possibility because it may occur as a dust and because it can be oxidized in the presence of moisture to form 1,4-benzoquinone, which is more volatile. The saturated concentration in air for hydroquinone vapor under standard conditions is estimated to be 0.108 mg/m^3 (approximately 0.024 ppm at 25°C) (NIOSH, 1978).

Hydroquinone reacts with molecular oxygen (autooxidation), in the course of which hydrogen peroxide may be generated (WHO, 1994). Autooxidation of hydroquinone is not synonymous with semiquinone auto-oxidation, which is also termed quinone redox cycling. The latter phenomenon entails redox cycling between a semiquinone (e.g., *p*-benzosemiquinone) and quinone in the presence of molecular oxygen, generating the superoxide anion radical. The addition of superoxide dismutase (SOD), which catalyzes the dismutation of superoxide anion radical to H_2O_2 and O_2 to media in which this cycling is occurring, drives the autooxidation of *p*-benzosemiquinone to *p*-benzoquinone by removal of superoxide anion radical (Winterbourn, 1981; Rossi et al., 1986).

B. Human Exposure

Hydroquinone is a synthetic agent with a wide range of commercial applications. It is used as a photographic developer (with black-and-white film), a dye intermediate, as a stabilizer in paints, varnishes, motor fuels, and oils, and as an antioxidant in the rubber industry. Older estimates of hydroquinone in air suggested that concentrations were in the range of 2–5 mg/m^3 during manufacture and use, but could reach as high as 20–35 mg/m^3 (O'Donoghue et al., 1995; Oglesby et al., 1947). With the introduction of effective dust control measures, routine monitoring of occupational settings had shown a general average of ca. 0.10–0.50 mg/m^3 (U.S. EPA, 1987). In the neighborhood of photographic development processes air concentrations of <0.01 mg/m^3 are common (Friedlander et al., 1982). Most current regulatory limits (e.g., 8-h time-weighted average threshold limit values for occupational air exposure) are 2 mg/m^3 (WHO, 1994).

Exposure to skin is mainly, but not entirely, a result of its medicinal usage. As such, hydroquinone is normally applied once per day as a 2% cream, although creams containing up to 10% hydroquinone may be used. The treatment area is frequently the face in treatment of melasma or postinflammatory hyperpigmentation consequent to acne. In such circumstances,

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A Study of Developmental Toxicity of Hydroquinone in the Rabbit[1,2,3]

S. J. MURPHY,*[,4] R. E. SCHROEDER,† A. M. BLACKER,‡ W. J. KRASAVAGE,§ AND J. C. ENGLISH§

*Department 459B, Toxicology & Regulatory Compliance, The Goodyear Tire & Rubber Company, Akron, Ohio 44305; †Reproduction/Teratology, Bio/dynamics, Inc., East Millstone, New Jersey 08875-2360; ‡Rhone-Poulenc Inc., Research Triangle Park, North Carolina 27709; and §Health and Environment Labs, Eastman Kodak Company, Rochester, New York 14652-3615

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To obtain information on potential developmental toxicity, hydroquinone (HQ) was administered to pregnant New Zealand White rabbits (18 mated per dose group) in aqueous solution (0, 25, 75, or 150 mg HQ/kg/day) by gavage on Gestation Days (GD) 6 to 18. Caesarean sections were performed on GD 30. Doses of 75 and 150 mg/kg/day adversely affected feed consumption and/or body weights of dams during the treatment period. At these doses, however, treatment-related effects were not evident from physical observations, liver and kidney weights, premature delivery incidence, and caesarean sectioning data. The NOEL for maternal toxicity was 25 mg/kg/day. In the 150 mg/kg/day dose group, total incidences of external, visceral, and skeletal findings for fetuses did not differ statistically from controls. Slight, statistically insignificant, increases were found, however, in the incidences of ocular and minor skeletal malformations (microophthalmia, vertebral/rib defects, angulated hyoid arch) on both a per fetus and a per litter basis. Under the conditions of this study, HQ at 150 mg/kg/day produced minimal developmental alterations in the presence of maternal toxicity. The NOEL for developmental toxicity was 75 mg/kg/day.
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Hydroquinone (HQ, CAS No. 123-31-9) is a white crystalline solid used industrially as an antioxidant, as a stabilizing agent for some polymers, and as an intermediate in the manufacturing of dyes and pigments. It is also used as a developing agent in black and white photographic processing. In the cosmetic industry, small amounts are used in dermatologic preparations and in hair dyes (USEPA, 1985). HQ has been found as a product of combustion in the mainstream smoke of nonfiltered cigarettes (NTP, 1990). In nature, it is found in bearberry, mountain cranberry, and whortleberry leaves and in the bark and buds of pear trees (NIOSH, 1978).

In 1985, the U.S. Environmental Protection Agency (EPA) issued a Final Test Rule for HQ under Section 4(a) of the Toxic Substances Control Act. Because the Agency believed existing data were inadequate to allow an evaluation of the developmental toxicity potential of HQ, the rule indicated HQ should be tested in one nonrodent and in one rodent species.

At that time, no developmental or reproductive toxicity studies had been conducted in the rabbit, but several had been conducted in the rat. In one of these studies, administration of 50–200 mg HQ/kg/day by gavage reportedly prolonged the diestrus phase of the esterous cycle (Racz *et al.*, 1958). In a study with Walter Reed-Carworth Farm strain rats (Telford *et al.*, 1962), 10 females ingesting a total of 0.5 g HQ (calculated to be approximately 115 mg/kg/day) in the diet throughout gestation had an increased incidence of fetal resorptions (26.8%) when compared to 126 control females (10.6%). All 10 HQ-treated rats exhibited resorptions compared to 40.8% of the control animals. In a study reported by Ames *et al.* (1956), 3000 ppm HQ (calculated to be approximately 225 mg/kg/day) administered in the diet 10 days before and during (implied) gestation did not adversely affect fertility, gestation length, mean litter size, viability, or lactation indices of 10 treated rats when compared with 16 control females. In the studies reviewed above, offspring were probably examined externally but not internally; no evidence of a possible teratogenic effect was reported. Since 1985, results of three reproductive/developmental toxicity studies of HQ in the rat have been published (Kavlock, 1990; Blacker *et al.*, 1991; Krasavage *et al.*, 1991).

The present study was conducted to determine whether HQ would produce adverse developmental effects in the rabbit. It was sponsored by the Chemical Manufacturers Association HQ Panel and was conducted to fulfill the require-

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[2] This work was supported by the Chemical Manufacturers Association Hydroquinone Panel whose member companies are Eastman Kodak Company, The Goodyear Tire & Rubber Company, Rhone-Poulenc Inc., and Mitsui Petrochemical Industries, Ltd.

[3] This study was designed to meet requirements established by EPA according to published TSCA protocol guidelines as presented in FR Vol. 50, No. 188, P. 39433 and revised in FR Vol. 52, No. 97, p. 19,077.

[4] Present address: 231 Christopher Crescent, Saskatoon, Saskatchewan S7J3R5, Canada.

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James W. Pifer · F. Terry Hearne · Frank A. Swanson
John L. O'Donoghue

Mortality study of employees engaged in the manufacture and use of hydroquinone

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Abstract Mortality in a 1942–1990 cohort of 858 men and 21 women employed in the manufacture and use of hydroquinone was evaluated through 1991. Average exposure concentrations, 1949–1990, ranged from 0.1 to 6.0 mg/m^3 for hydroquinone dust and from less than 0.1 to 0.3 for quinone vapor (estimated 8-h time-weighted averages). Compared with general population and occupational referents, there were statistically significant deficits in total mortality and deaths due to cancer. No significant excesses were observed for such hypothesized causes as kidney cancer [2 observed vs 1.3 expected (both control groups), $P \sim 0.39$], liver cancer (0 vs 0.8, 1.3), and leukemia (0 vs 2.3, 2.7). Dose-response analyses of selected causes of death, including renal carcinoma, demonstrated no statistically significant heterogeneities or linear trends according to estimated career hydroquinone exposure (mg/m^3-years) or time from first exposure.

Key words Hydroquinone · Quinone · Occupational mortality · Cancer · Toxicologic review

Introduction

Hydroquinone (HQ; 1,4-benzenediol) is a white crystalline compound used extensively as a developer for black-and-white photography, medical and industrial X-ray films, and graphic arts films. Major nonphotographic applications include use as an antioxidant and antiozonant for rubber, a polymerization inhibitor for acrylic and vinyl acetate monomers, and an intermediate for agrochemicals, performance plastics, and dyes. HQ is also an ingredient of dermatologic preparations used to lighten hyperpigmented areas. Quinone (BQ; *p*-benzoquinone), a yellowish crystalline solid that readily sublimes, is utilized primarily as an intermediate in agrochemical manufacturing. It is also used in the dye, textile and chemical tanning industries and for the production of unsaturated polyesters. In addition to being an intermediate for the HQ aniline oxidation process, BQ is an in vivo metabolite of HQ.

Case reports and clinical studies have described ocular effects in HQ production workers. Exposure to relatively high concentrations of HQ dust and BQ vapor in older manufacturing operations has been associated with both temporary and permanent eye effects, including irritation, conjunctival and corneal pigmentation, and corneal opacities and structural irregularities (e.g., erosion of the epithelium and changes in the thickness and curvature of the cornea), which resulted in loss of visual acuity in a few severe cases [2, 3]. The earliest report of conjunctival staining was observed after only 4 months of exposure; no cases of corneal involvement occurred in less than 5 years [55]. There was evidence of greater severity of response with increasing duration of employment, albeit there was considerable individual variability. Although BQ vapor was hypothesized as the major etiologic factor, HQ dust was considered a contributory cause.

A few cases of a vitiligo-like depigmentation have been described among film processing workers handling developing solutions containing HQ [14, 15, 36, 40]. In addition, Choudat et al. [10] reported respiratory effects in a group of employees exposed simultaneously to a number of chemicals, including HQ and its derivatives.

The work was done at Eastman Kodak Company (Rochester, N.Y., USA).

J.W. Pifer (✉) · F.T. Hearne
Epidemiology Section, Building 320, Kodak Park, Eastman Kodak Company, Rochester, NY 14652–6253, USA

F.A. Swanson
Industrial Hygiene Section, Tennessee Eastman Division, Eastman Chemical Company, Kingsport, Tenn., USA

J.L. O' Donoghue
Corporate Health and Environment Laboratories, Corporate Health, Safety and Environment, Eastman Kodak Company, Rochester, N.Y., USA

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Metabolic Rate Constants for Hydroquinone in F344 Rat and Human Liver Isolated Hepatocytes: Application to a PBPK Model

Torka S. Poet,*[,1] Hong Wu,* J. Caroline English,† and Richard A. Corley*

*Battelle, Pacific Northwest Division, Center for Biological Monitoring and Modeling, P.O. Box 999, Richland, Washington 99352; †Health and Environmental Laboratories, Eastman Kodak Companies, Rochester, New York 14652

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Hydroquinone (HQ) is an important industrial chemical that also occurs naturally in foods and in the leaves and bark of a number of plant species. Exposure of laboratory animals to HQ may result in species-, sex-, and strain-specific nephrotoxicity. The sensitivity of male F344 versus female F344 and Sprague-Dawley rats or B6C3F1 mice appears to be related to differences in the rates of formation of key nephrotoxic metabolites. Metabolic rate constants for the conversion of HQ through several metabolic steps to the mono-glutathione conjugate and subsequent detoxification via mercapturic acid formation were measured in suspension cultures of hepatocytes isolated from male F-344 rats and humans. A mathematic kinetic model was used to analyze each metabolic step by simultaneously fitting the disappearance of each substrate and the appearance of subsequent metabolites. An iterative, nested approach was used whereby downstream metabolites were considered first, and the model was constrained by the requirement that rate constants determined during analysis of individual steps must also satisfy the complete, integrated metabolism scheme, including competitive pathways. The results from this study indicated that the overall capacity for metabolism of HQ and its mono-glutathione conjugate is greater in hepatocytes from humans than in those from rats, suggesting a greater capacity for detoxification of the glutathione conjugates in humans. Metabolic rate constants were applied to an existing physiologically based pharmacokinetic model, which was used to predict total glutathione metabolites produced in the liver. The results showed that body burdens of these metabolites will be much higher in rats than in humans.

Key Words: **physiological model; bioactivation; nephrotoxicity; species-specific.**

Hydroquinone (HQ) is present in natural products such as wheat and some types of fruit, and it is used in photographic developing solutions, in rubber and vinyl monomer manufacturing (Deisinger *et al*., 1996), and in naturopathic remedies as an antioxidant (Wittig *et al*., 2001). In addition, HQ is a metabolite of the industrial solvent, benzene, as recently reviewed by Lovern *et al*. (1999). A consequence of the industrial, consumer, and natural sources of HQ is a high potential for low-level human exposures.

Two chronic bioassays (NTP 1989; Shibata *et al*., 1991) with HQ have indicated increases in the severity of chronic nephropathy and renal adenomas in male F-344 rats in regions of the kidney that were significantly affected by chronic progressive nephropathy (Whysner *et al*., 1995; Hard *et al*., 1997). Marked gender and species differences in the nephrotoxicity of HQ have been noted. Long-term exposure studies indicate that the kidneys of male F-344 rats are more susceptible to adverse effects associated with HQ exposure than kidneys in female rats, other strains of rats, mice, or dogs (Boatman *et al*., 1996; English *et al*., 1994; NTP 1989; Shibata *et al*., 1991). In a retrospective study on human mortality from subjects working in an HQ manufacturing plant, no increase in mortality was attributable to renal disease or tumors (Pifer *et al*., 1995).

The mechanism of HQ-induced nephropathy and the gender, strain, and species differences in susceptibility have not been fully elucidated. The gender difference may simply be due to spontaneous nephropathy progressing more rapidly in male than female rats (Sandberg *et al*., 2003; Seely *et al*., 2002). In addition, species differences in metabolism may be a factor in the extent of nephrotoxicity resulting from HQ exposures. Metabolism to reactive intermediates is clearly a factor in the renal toxicity and exacerbation of chronic progressive nephropathy associated with HQ ingestion in laboratory animals. While glucuronide and sulfate conjugation are the primary pathways for detoxification, accounting for as much as 90–99% of the administered dose in rats, the minor glutathione conjugation pathway appears to be responsible for renal toxicity and, ultimately, tumorigenicity (DeCaprio 1999). Other studies have indicated that benzoquinone might represent a reactive and mutagenic metabolite, but the processing of DNA damage appears to be different in human and mouse cells (Nakayama *et al*., 2000). Gender-specific enzyme induction after repeated dosing may also be a factor (Boatman *et al*., 1996).

The complex metabolism and associated toxic potential of specific HQ metabolites epitomizes the importance of understanding the balance between species-, strain- and gender-specific activation versus detoxification pathways. A simplified

[1] To whom correspondence should be addressed at Battelle, Pacific Northwest Division, P.O. Box 999, MSIN P7-59, Richland, Washington 99352. Fax: (509) 376-9064. E-mail: torka.poet@pnl.gov.

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Refinement of Hydroquinone PBPK Model and its Use for Dermal Exposure Assessment

Authors

Torka S. Poet[1], Betsy D. Carlton [2], James A. Deyo[3], and Paul M. Hinderliter[1]

[1]Battelle, Pacific Northwest Division, Center for Biological Monitoring and Modeling, PO Box 999, Richland, WA 99352, USA

[2]Rhodia, Inc. Toxicology. 5171 Glenwood Ave, Raleigh, NC 27612, USA

[3]Eastman Chemical Company, 100 N. Eastman Rd, Kingsport, TN 37662

Running Title

Hydroquinone PBPK Model

Corresponding Author:

Torka S. Poet, Ph.D.

Battelle, Pacific Northwest Division

PO Box 999, MSIN P7-59

Richland, WA 99352, USA

Tel: 509 376 7740

Fax: 509 376 9064

torka.poet@pnl.gov

Key Words: Physiologically based pharmacokinetic model, risk assessment, dermal absorption, in vitro/in vivo extrapolation.

Abbreviations: benzoquinone (BQ), hydroquinone (HQ), HQ-Cysteine (HQ-Cys), hydroquinone mono-glutathione conjugate (HQ-SG), percutaneous permeability coefficient (Kp) physiologically based pharmacokinetic (PBPK).

Abstract

A physiologically based pharmacokinetic (PBPK) model for hydroquinone (HQ) was refined to include an expanded description of HQ glucuronide metabolites and a description of dermal exposures to support route-to-route and cross-species extrapolation. Total urinary excretion of metabolites from *in vivo* rat dermal exposures was used to estimate a percutaneous permeability coefficient (K_p; $3.6x10^{-5}$). The human *in vivo* K_p was estimated to be $1.62x10^{-4}$ cm/hr, based on *in vitro* skin permeability data in rats and humans and the rat *in vivo* values. The projected total multi-substituted glutathione (which was used an internal dose surrogate for the toxic glutathione metabolites) was modeled following an exposure scenario based on submersion of both hands in a 5% aqueous solution of HQ (similar to black and white photographic developer use solution) for 2 hr, a worst-case exposure scenario. The total multi-substituted glutathione following this human dermal exposure scenario was several orders of magnitude lower than the internal total glutathione conjugates in rats following an oral exposure to the rat NOEL of 20 mg/kg. Thus, under more realistic human dermal exposure conditions, it is unlikely that toxic glutathione conjugates (primarily the di- and, to a lesser degree, the tri-glutathione conjugate) will reach significant levels in target tissues.